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Copper-catalyzed asymmetric allylic substitution reactions with organozinc and Grignard reagents*

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Abstract: Asymmetric allylic alkylations (AAAs) are among the most powerful C–C bond-forming reactions. We present a brief overview of copper-catalyzed AAAs with organometallic reagents and discuss our own contributions to this field. Work with zinc reagents and phosphoramidite ligands provided a framework for later developments which employ Grignard reagents and ferrocenyl ligands. High yields and excellent regioselectivities and enantioselectivities are achieved. The AAAs may be more general than previously envisioned, in terms of using substrates functionalized with heteroatoms at various positions; heteroatom substituents at the γ-position provide densely functionalized building blocks. These *h*-AAA reactions rely on the design of appropriate substrates containing heteroatoms and have allowed us to demonstrate viable new approaches toward the synthesis of versatile organic building blocks. We illustrate that the chiral secondary allylic alcohols, primary homoallylic alcohols and amines can readily be obtained in high enantiomeric purity in a catalytic asymmetric fashion by copper-catalyzed AAAs. Furthermore, we show that manipulation of the terminal olefin provides chiral building blocks where the ee of the starting materials is preserved.

Keywords: synthesis; asymmetric; catalysis; allylic; alkylations.

INTRODUCTION

The development of catalytic asymmetric versions of fundamental organic transformations has been a major goal for several years. Much of our effort has focused on copper-catalyzed additions of hard nucleophiles to electrophiles, especially C–C bond formation using asymmetric 1,4-additions to prochiral α,β-unsaturated carbonyl compounds [1–4]. This paper presents a brief overview of a related transformation — copper-catalyzed asymmetric allylic alkylations (AAAs) with organometallic reagents [1,5,6] followed by a discussion of our own contributions to this emerging field. These powerful reactions have been the subject of extensive studies and allow access to valuable synthons that are often used in the synthesis of complex natural products and molecules of pharmaceutical interest.

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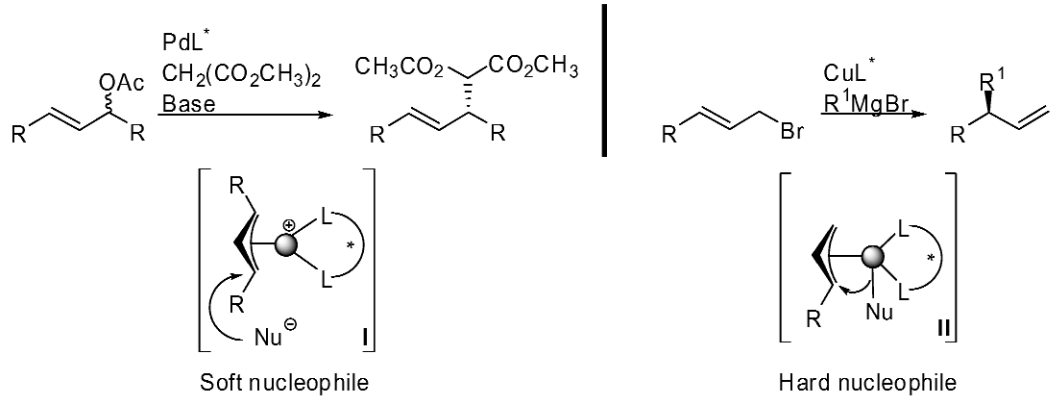
Our long-term goal is to develop practical asymmetric catalytic methods that allow access to versatile building blocks for synthesis. Such methods would provide alternatives to, and complement, existing chiral pool or chiral auxiliary strategies and classical resolution techniques. The fact that more widespread use of catalytic approaches, the so-called "catalytic switch", over noncatalytic (stoichiometric) synthesis has been limited is due to the fact that asymmetric catalytic methods are frequently developed using benchmark substrates and not on substrates that provide building blocks used in actual synthesis [7]. Our approach is to actively develop catalyst systems that achieve fundamental transformations on nontrivial substrates.

OVERVIEW

The development of highly enantioselective transition-metal-catalyzed allylic alkylation reactions has enjoyed widespread attention the past decades [1,5,6,8,9]. The palladium-catalyzed substitution reactions using soft nucleophiles are well understood. The classical Trost-type AAA is given on the left-hand side of Scheme 1 [10]. Hard organometallic nucleophiles, which can directly introduce simple alkyl groups, have been used to a much more limited extent [6]. Distinct mechanisms are proposed for the metal-catalyzed allylic alkylation reactions with hard and soft nucleophiles. In palladium-catalyzed reactions, the soft nucleophile [11,12] will approach the allyl moiety from the opposite side of the coordinated metal ion (see intermediate **I**), where with hard nucleophiles reductive elimination (see intermediate **II**) results in C–C bond formation (vide infra).



Scheme 1 Allylic substitution reaction pathway for soft and hard nucleophiles.

A brief survey of the contributions of several groups to copper-catalyzed AAA reactions, subject of recent reviews [5,6], is presented in Fig. 1. The groups of Bäckvall and van Koten [13] were the first to report AAAs in 1995 using Grignard reagents and allylic acetates (42 % ee) later [14] improved upon by using the ferrocenyl ligands shown in Fig. 1. Knochel's work [15] illustrated that bulky dialkylzinc reagents were also suitable nucleophiles. In 2001, our group [16] and the Alexakis group [17] used phosphoramidites in combination with linear dialkylzinc and Grignard nucleophiles, respectively. Modular peptide-based ligands developed by Hoveyda et al. [18,19] provide highly effective catalysts for a number of different substrates using organozinc compounds; these methods also provide access to quaternary centers. More recently, it has been shown by Okamoto [20] that chiral nonracemic *N*-heterocyclic carbene (NHC) ligands promote substitutions by Grignard reagents. Hoveyda [21] has illustrated that bidentate NHC ligands allow highly efficient and selective substitution with dialkyl zinc reagents. While these ligands provide the most promising methods, the Woodward group [22] has shown that

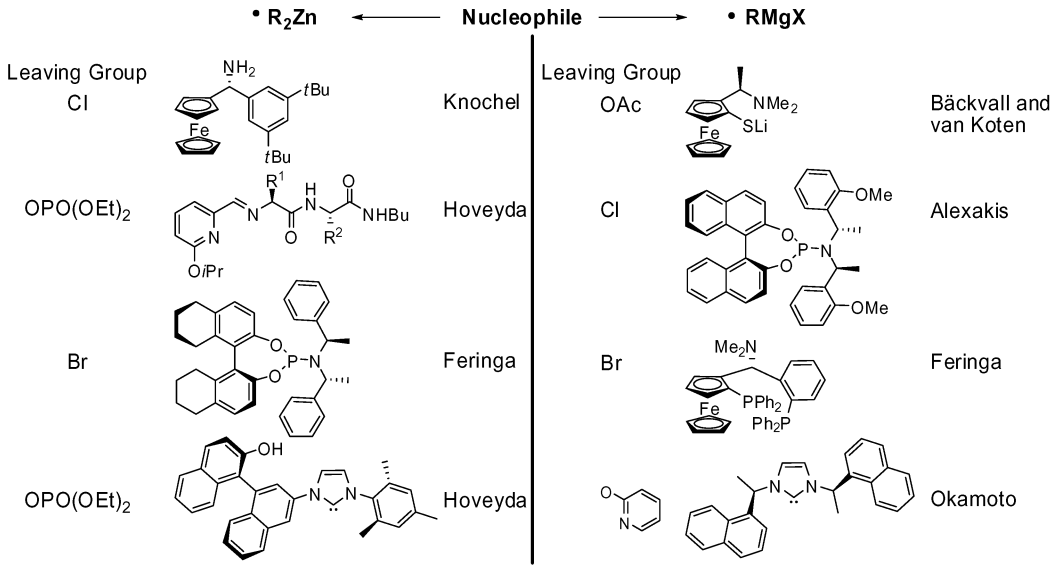


Fig. 1 AAA with zinc and Grignard reagents.

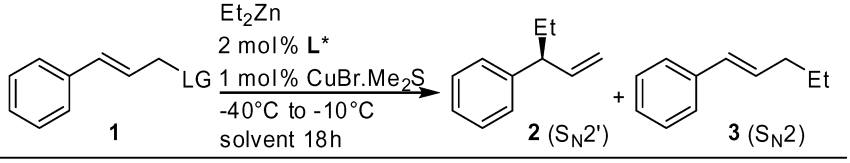
simple BINOL and amine-derived ligands can promote related asymmetric substitutions with alkyl zinc reagents.

RESULTS AND DISCUSSION

AAAs with organozinc reagents and phosphoramidite ligands

Several years ago, our catalysts for AAAs were based on the copper-phosphoramidite system that we successfully applied to asymmetric 1,4-additions [3]. Preliminary experiments, involving cinnamyl chloride, diethylzinc, and CuBr·SMe_2, provided the desired S_N2' product in modest (3:1) regioselectivity and 17 % ee (Table 1). Screening various solvents showed that coordinating ethers improved the enantioselectivity, and diglyme was chosen for further experiments even though THF gave better regioselectivities. Using these conditions, a set of readily available leaving groups (cinnamyl acetates, phosphorus esters, and halides) were tested. Only allyl halides were found to react with R_2Zn reagents, with the allyl bromides providing the best results (up to 77 % ee, see Table 1).

Table 1 Copper-catalyzed AAA with organozinc reagents.

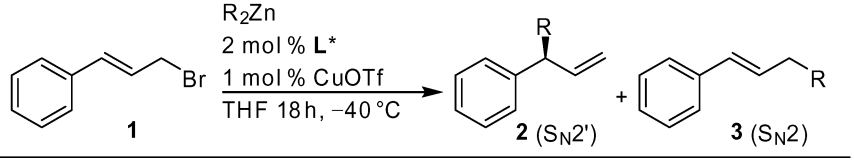


entry	LG	solvent	**2**:**3**	convn(%)	yield(%)	ee of **2**(%)
1	Cl	THF	75:25	70	nd	17
2	Cl	diglyme	57:43	90	57	28
3	I	diglyme	66:34	90	24	63
4	Br	diglyme	84:16	70	54	77

This relatively selective catalyst gave the highest reported ee at the time for linear dialkylzinc reagents [16], providing a major lead to further improve the AAA conditions. In the initial system, diglyme was used as the solvent, which was of limited use due to its freezing point (−64 °C), so we turned our attention to optimizing the reaction in solvents that can be applied at lower temperatures.

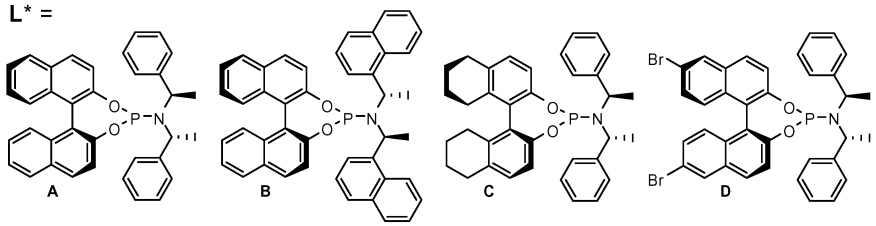
Screening revealed that the CuOTf-THF combination gave acceptable (69 %) enantioselectivities and even higher S_N2':S_N2 ratios (75:25) than those observed in diglyme (57:43). Ligand screening, carried out using 1 mol % of CuOTf and 2 mol % of a variety of monodentate phosphoramidites, illustrated that in general those with a BINOL-type backbone were the most effective (for examples, see Table 2, entries 1–4) [23].

Table 2 Copper-catalyzed AAA with organozinc reagents.



entry	R	L*	**2**:**3**	yield(%)	ee of **2**(%)
1	Et	**A**	85:15	96	69
2	Et	**B**	94:6	74	75
3	Et	**C**	91:9	95	82
4	Et	**D**	83:17	76	65
5[a]	Et	**C**	93:7	74	86
6[a]	*i*-Pr	**C**	97:3	94	88
7[a]	*n*-Bu	**C**	91:9	58	87

L* =



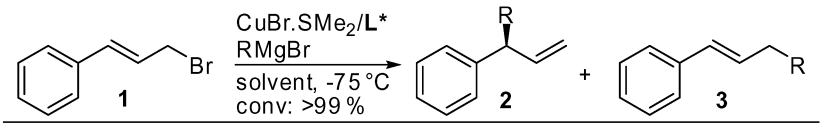
[a]T = –60 °C.

With this phosphoramidite ligand system in hand we were able to perform catalytic asymmetric alkylations with several organozinc reagents (Table 2, entries 5, 6 and 7). We tested several types of substrates in this reaction and found that although substituted cinnamyl bromides performed equally well, this methodology appeared limited to cinnamyl substrates. With the prospect of developing a general method for these transformations, we next explored Grignard reagents. In contrast to zinc reagents, a wide variety of Grignard reagents are commercial available. An additional benefit of using Grignard reagents is that they are easily handled and can be readily made in situ from alkyl halides.

AAAs with Grignard reagents and ferrocenyl-based ligands

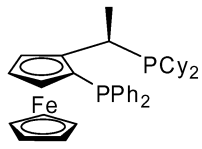
Recently, we have shown that the combination of copper salts and ferrocenyl ligands resulted in highly effective catalysts for asymmetric 1,4-additions to cyclic and acyclic α,β-unsaturated compounds [1]. The use of Josiphos and CuBr·SMe_2 in *t*-BuOMe (see Table 3, entry 1) allowed the addition of MeMgBr to aromatic allyl bromides with high regioselectivity (85:15) and enantioselectivity (85 %) [24].

Table 3 Copper-catalyzed AAA with Grignard reagents.

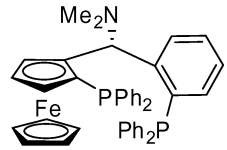


entry	R	L*	solvent	2 : 3	ee(%)
1	Me	**E**	*t*-BuOMe	85:5	85
2	Et	**E**	*t*-BuOMe	38:62	56
3	Et	**F**	*t*-BuOMe	31:69	32
4	Et	**F**	CH_2Cl_2	82:18	96

L* =



(*R*,*S*)-Josiphos **E**



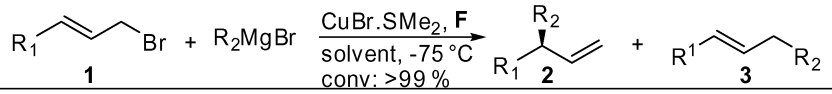
(*R*,*S*)-Taniaphos **F**

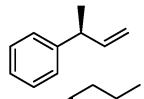
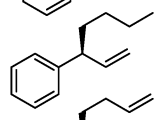
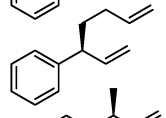
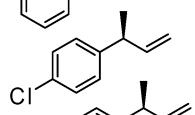
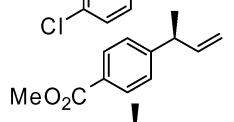
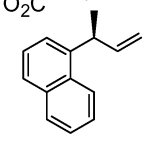
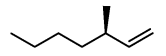
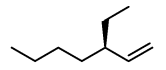
While this system gives access to optically enriched products, the use of other Grignard reagents, for example, EtMgBr (56 % ee, entry 2), was problematic. A detailed optimization was undertaken using Josiphos as the ligand, but in the event we found that another ferrocenyl ligand, Taniaphos, gave a much more versatile and generally applicable system. While changing the copper source did not improve selectivities, the solvent had a dramatic effect. Dichloromethane was the solvent of choice, affording the desired products with high regioselectivities (82:18) and ee (96 %) in the case of EtMgBr, while catalyst loadings as low as 1 mol % are tolerated.

With the Taniaphos-based catalyst system in hand, allylic substitutions could be performed on aromatic substrates with a wide variety of Grignard reagents, providing the corresponding products (**2a–f**, Table 4) with high regioselectivities and excellent enantioselectivities (94–98 % ee). The ability to add MeMgBr with nearly absolute stereocontrol is particularly noteworthy.

Examination of the linear aliphatic allylic bromides **1e**, under these reactions conditions, illustrated that such materials are also excellent substrates, affording almost exclusively the branched products **2g** and **2h** with high enantioselectivities (92 and 93 %, respectively, entries 8 and 9). We have shown that products **2** (Table 4) can be used in further reactions, specifically cross metathesis with acrylates followed by 1,4-addition on the resulting α,β-unsaturated species, to provide linear, 1,2-disubstituted alkyl arrays [24].

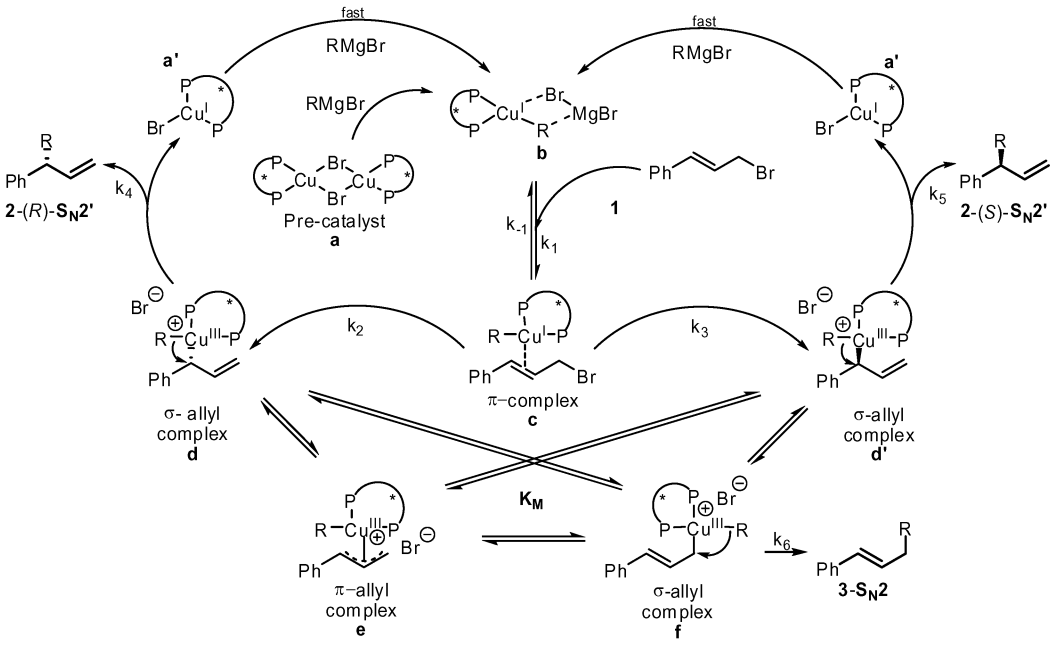
Table 4 Copper-catalyzed AAA with a variety of Grignard reagent and substrates.



entry	R_1	R_2	**2**		yield(%)	**2** : **3**	ee(%)
1	**1** Ph	Me	**a**		91	97:3	98
3	**1** Ph	C_4H_9	**b**		92	87:13	94
4	**1** Ph	C_4H_7	**c**		93	91:9	95
5	**1b** *p*ClPh	Me	**d**		95	99:1	97
6	**1c** *p*MeO_2CPh	Me	**e**		94	98:2	97
7	**1d** 1-Napht	Me	**f**		87	>99	96
8	**1e** *n*-Bu	Me	**g**		99	>99	92
9	**1e** *n*-Bu	Et	**h**		99	>99	93

In entries 8 and 9, the yield was determined by GC analysis of the crude reaction mixture.

The reaction likely proceeds through the catalytic cycle shown in Scheme 2. Our previous mechanistic work on Grignard additions involving similar ferrocene copper complexes illustrated that the initially formed precatalyst **a** reacts readily with Grignard reagents, forming the catalytically active species **b** [25]. Initial π-complexation of Cu^I to the allylic double bond followed by S_N2'-type oxidative addition to form the σ-complex is likely the next step and has strong mechanistic support in the literature [26,27]. The diastereomeric σ-allyl-Cu^{III} intermediates **d** or **d'** then can undergo reductive elimination (k_4 or k_5), leading to formation of the desired S_N2' product and mononuclear Cu^I species **a'**. By analogy to our mechanistic work on the catalytic asymmetric 1,4-addition [25], it is likely that the irreversible reductive elimination of intermediates **d** or **d'** is the rate-determining step. Theoretical work has suggested that such reductive eliminations may occur through an enyl [σ+π]-type structure rather than the more traditional intermediates depicted here, however, conventional notations cannot easily deal with such bonding [28]. Alternatively, isomerization, presumably through π-allyl-Cu^{III} species **e**, can degrade the selectivity by producing **d**, **d'**, or **f**. Isomerization to **d** and **d'** may lead to erosion of enantioselectivity depending on the relative rates of k_4 and k_5 with respect to oxidative addition (k_2 and/or k_3). Isomerization to species **f** may lead to poor regioselectivity, depending on the rate of k_6 relative to other rates, as the reductive elimination of **f** leads to the product of a formal S_N2 addition.

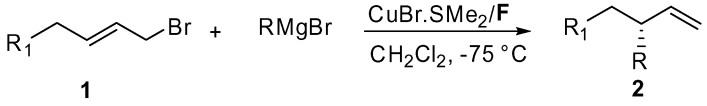


Scheme 2 Catalytic cycle for copper-catalyzed AAA reactions with Grignard nucleophiles.

Application toward chiral building blocks

Much to our delight, substrates containing oxygen or nitrogen functionalities embedded in the starting material worked equally well (Table 5) [29]. We ran several of these reactions on a preparative scale (7.5 mmol) with no loss of yield or regio- or enantioselectivity. The presence of a benzyloxy group in substrate **1f** was tolerated, and a variety of linear (Me, Et, *n*-Bu, *n*-Pent) and functionalized (3-butenyl

Table 5 Copper-catalyzed AAA on substrates bearing a functional group at the δ-position with a variety of Grignard reagents.



1 **2**

1f R_1 = OBn; **1g** R_1 = OTBDPS; **1h** R_1 = N(Tos)Boc

entry	1	RMgBr	2	yield(%)	ee(%)
1	**f**	Me	**i**	94	92
2	**f**	Et	**j**	98	94
3	**f**	*n*-Pent	**k**	87	90
4	**f**	*n*-Bu	**l**	93	94
5	**f**	3-Butenyl	**m**	89	94
6	**f**	$Ph(CH_2)_2$	**n**	86	92
7	**g**	Me	**o**	72	94
8	**h**	Me	**p**	96	95
9	**h**	Et	**q**	83	90

and phenylethyl) Grignard reagents can be added with equal efficiency, providing excellent building blocks (**2i–n**) for natural product synthesis. Use of the bulky TBDPS protecting group **1g** was also tolerated (Table 5, entry 7) and in the case of MeMgBr leads to slightly higher (94 %) enantioselectivity, albeit lower (72 %) yield compared to the benzyl-protected substrate. A double-protected amine moiety **1h** (Table 5, entries 8 and 9) is also compatible with the system (MeMgBr, 96 % yield, >20:1 regioselectivity, 96 % ee). These studies illustrate that chiral primary alcohols and amines can readily be obtained in high enantiomeric purity in a catalytic asymmetric fashion [29].

Having demonstrated that the catalyst can be applied to allylic bromides with protected alcohols and amines at the δ-position, we turned our attention to converting these products into building blocks frequently used in complex molecule synthesis (i.e., to have access to a collection of multifunctional chiral synthons). We carried out straightforward transformations of the terminal olefin to provide, among others, the valuable chiral building blocks shown in Fig. 2 [29]. In all cases, the ee of the starting materials was preserved. This work demonstrates that these alkylations provide a highly practical catalytic alternative to common approaches to such chiral synthons, which rely on the use of materials derived from the chiral pool or obtained via classical resolution techniques.

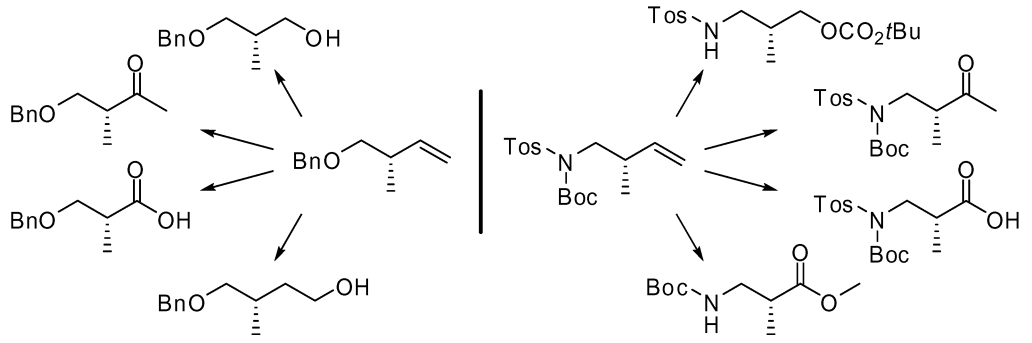


Fig. 2 Multifunctional building blocks from AAA products.

Development of the *hetero*-allylic asymmetric alkylation (*h*-AAA) reaction

Encouraged by the above reactions, which tolerate heteroatoms and provide functionalized products, we envisioned a new reaction based on allylic alkylation, where a simple organometallic reagent adds to an allylic substrate bearing a heteroatom directly at the γ-position. Such a reaction, a *hetero*-allylic asymmetric alkylation (*h*-AAA, Fig. 3) [30], would provide a highly versatile addition to the current synthetic repertoire for the production of valuable building blocks.

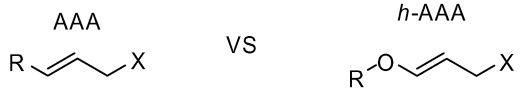
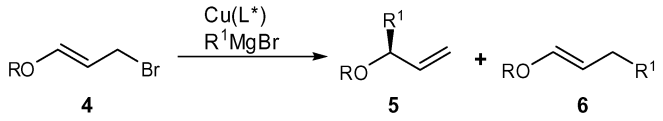


Fig. 3 AAA vs. *h*-AAA.

This reaction, in the case of a γ-oxygen substituent (RO, Fig. 3), may provide enantiomerically pure allylic alcohols: key building blocks in numerous synthetic applications. These alcohols are usually prepared from the chiral pool [31], by kinetic resolution [32–34] and more recently by allylic substitution with oxygen nucleophiles [35–38]. We anticipated that 3-bromopropenyl alcohols **4** (Scheme 3) would be viable substrates if a suitable value for R could be found. Compound **4** contains a leaving group with a neighboring vinylogous oxygen functionality, and R would need to be suffi-

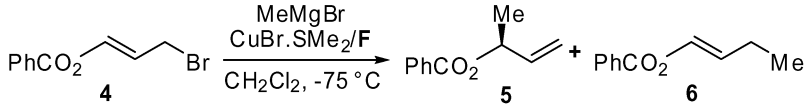


Scheme 3 Copper-catalyzed *h*-AAA reaction with Grignard nucleophiles.

ciently electron-withdrawing for the substrate to be stable. Furthermore, the protecting group R needs to be compatible with highly reactive RMgBr species. Finally, substrate **4** should also be readily available. We chose to explore 3-bromopropenyl esters (**4**, R = PhCO), available through simple condensation of an acyl bromide and an α,β-unsaturated aldehyde, even though ester groups are prone to attack by Grignard reagents.

When we submitted **4** (R = PhCO) to optimized allylic alkylation conditions (see above) and MeMgBr, we were gratified to obtain **5** in 85 % yield and 98 % ee (Table 6, entry 1). The reaction appeared to go with complete regioselectivity as **6** could not be detected by ^{1}H NMR spectroscopy (<1 % by HPLC analysis). Examination of variations of the catalyst system found the original catalyst system superior in all cases. In the standard procedure, 5 mol % catalyst loading is used but catalyst loadings as low as 0.05 mol % have been employed without detrimental effects [30].

Table 6 Copper-catalyzed *h*-AAA with MeMgBr.



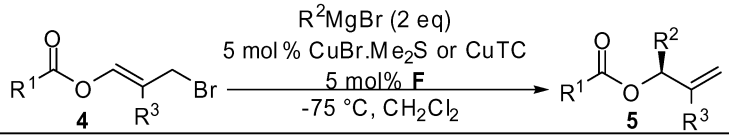
entry	temp[°C]	**5**:**6**	yield(%)	ee(%)
1	-74	99:1	85	(+)98
2[a]	-73	8:92	36	n.d.
3	-15	99:1	76	(+)90
4	-82	79:21	67	(-)94
5	-85	37:63	76	n.d.

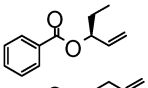
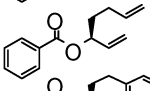
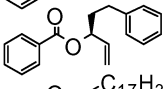
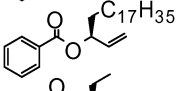
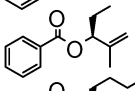
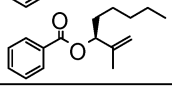
[a]*t*-BuOMe.

These procedures are valuable in that they illustrate that a *h*-AAA is possible. Further, they allow practical asymmetric synthesis of the simplest chiral allylic alcohols, such as 1-buten-3-ol. Such low-molecular-weight allylic alcohols have not been reported to be successfully resolved in the Sharpless epoxidation, and other asymmetric catalytic methods also do not allow their ready preparation [39].

The use of *t*-BuOMe as solvent, surprisingly, led largely (8:92, entry 2) to formation of the undesired regioisomer **6** at a relatively slow rate (36 % conversion, 12 h). Another curious case of regioselectivity reversal occurs upon cooling the reaction mixture below –80 °C. While at –74 °C the reaction provides exclusively **5**, at lower temperatures the undesired S_N2 adduct becomes prominent (Table 6, entries 1, 4, 5). These observations raised the question whether the formation of both **5** and **6** are copper-catalyzed. In the absence of copper, neither **5** nor **6** were formed in detectable (^{1}H NMR spectroscopy) levels. When the reaction was performed at higher temperatures, the enantioselectivity is largely preserved (90 % ee, unoptimized at –15 °C, entry 3), and the ester moiety displayed remarkable stability even with an excess of Grignard reagent.

Table 7 Copper-catalyzed *h*-AAA with a variety of Grignard reagents and substrates.



entry	R^1	R^2	R^3	**5**		yield(%)	ee(%)
1	Ph	C_2H_5	H	**5a**		87	98
2	Ph	C_4H_7	H	**5b**		96	97
3	Ph	C_8H_9	H	**5c**		93	93
4	Ph	$C_{18}H_{37}$	H	**5d**		93	>95
5	Ph(**4c**)[a]	C_2H_5	Me	**5e**		97 (2.5:1)	97
6	Ph(**4c**)[a]	C_5H_{11}	Me	**5f**		96 (2:1)	97

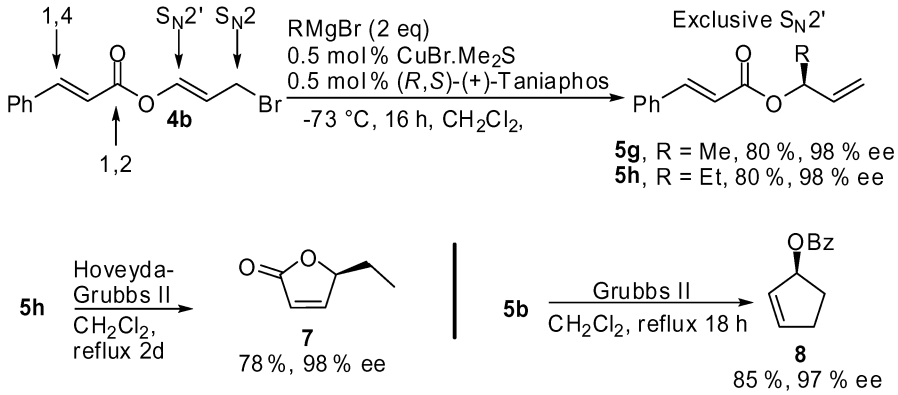
[a]Ligand = (*R*,*R*,*R*)-**A**, conditions [30,40].

A variety of Grignard reagents containing simple alkyl moieties, long alkyl chains, and functional groups that allow further manipulation (vide infra), were successfully added with excellent regio- and enantioselectivities (Table 7, entries 1–4). Current limitations of this catalyst system are substitution with sp^2-hybridized Grignard reagents, sp^3-hybridized secondary Grignard reagents, and sterically demanding Grignard reagents. These observations, in combination with results from similar catalyst systems in 1,4-additions led us to assume that these ferrocenyl-based catalysts do not tolerate sterically demanding nucleophiles or electrophiles.

In order to address these limitations, we examined less sterically demanding ligands. We were particularly interested in using β-substituted substrates (**4c**, R^3 = Me), as this would give products that cannot be obtained by further manipulation of the double bond. After judicious screening of ligands, copper sources, and solvents we found that CuTC combined with phosphoramidite (*R*,*R*,*R*)-**A** displayed good levels of selectivity. Slow addition, presumably preventing the formation of higher cuprates, of the Grignard reagent raised the asymmetric induction to excellent levels (ee: 97–98 %; Table 7, entries 5 and 6) however, only modest regioselectivities (2.5:1) were obtained.

In order to illustrate the applicability of the method to the synthesis of more complex molecules, we examined the reaction for a substrate containing potentially competitive functional groups. Cinnamyl derivative **4b**, readily prepared in one step, provided **5g**, with excellent regio- and enantioselectivities (>98:2, 98 % ee). It should be emphasized that the selectivity in this catalytic conversion is remarkable. Whereas substrate **4b** has α,β-unsaturated ester, enol ester, and allyl bromide moieties, and can undergo 1,4-addition, 1,2-addition, S_N2' and S_N2 substitution (among others), near-exclusive S_N2' substitution to a single enantiomer of **5g** takes place. Substitution with EtMgBr on **4b** similarly provided **5h** (80 % yield, 98 % ee; Scheme 4). This reaction was also run with 0.05 mol % catalyst loading with high enantioselectivity. These studies clearly demonstrate the versatility of the transformation, providing functionalized building blocks suitable for natural product synthesis.

Ring-closing metathesis (RCM) of **5h** to (*S*)-**7** (Scheme 4; 78 % yield, 98 % ee) was readily accomplished at reflux with Hoveyda–Grubbs II catalyst, despite having to overcome the activation bar-



Scheme 4 *h*-AAA followed by RCM; synthesis of optically pure building blocks **7** and **8**.

rier of cleaving the conjugated olefin, to produce butenolide **7**. This naturally occurring compound has been synthesized a number of times and a practical route (7 steps) to optically pure **7**, for use as a starting material in natural product synthesis, was developed by Takayama et al. [41]. When **5b** was subjected to RCM conditions with Grubbs II catalyst, carbocycle (*S*)-**8** [42] was obtained in 85 % yield and excellent ee (97 %, Scheme 4).

SUMMARY

Our recent efforts to develop new catalytic asymmetric C–C bond formation began, in case of the AAA, with zinc reagents and phosphoramidite ligands. The results provided a framework for later developments which employ easily handled Grignard reagents and commercial ferrocenyl ligands. The studies with Grignard reagents illustrate that high yields, regioselectivities, and enantioselectivities can be achieved. Our attempts to extend the scope of these reactions, in terms of using substrates functionalized with heteroatoms at various positions, has been highly successful and we have demonstrated alternative approaches toward the synthesis of versatile organic building blocks. These reactions provide a broader reaction scope than previously observed for AAAs, and we have made significant progress in control over regio- and enantioselectivity.

Our work illustrates that AAA reactions may be far more general than previously envisioned. Proof of concept of the *h*-AAA reaction illustrates that densely functionalized valuable building blocks, with high ee, may easily be achieved through a new type of reaction, that relies on the design of appropriate substrates. Since this publication [30], *h*-AAA reactions have been reported with substrates containing boron [43] and silicon [44] at the γ-position. We can only assume that AAA reactions are much more general than we have shown here. We continue to develop new methods toward achieving the goal of a so-called "catalytic switch" over noncatalytic (stoichiometric) synthesis.

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